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Differences in Factors Associated With Preterm and Term Stillbirth: A Secondary Cohort Analysis of the DESiGN Trial

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Keywords: fetal growth restriction | perinatal death | premature birth | SGA | stillbirth | term birth

ABSTRACT

Objective: To identify whether maternal and pregnancy characteristics associated with stillbirth differ between preterm and term stillbirth.

Design: Secondary cohort analysis of the DESiGN RCT.

Setting: Thirteen UK maternity units.

Population: Singleton pregnant women and their babies.

Methods: Multiple logistic regression was used to assess whether the 12 factors explored were associated with stillbirth. Interaction tests assessed for a difference in these associations between the preterm and term periods.

Main Outcome Measure: Stillbirth stratified by preterm ($<37^{+0}$ weeks') and term (37^{+0}–42^{+6} weeks') births.

Results: A total of 195 344 pregnancies were included. Six hundred and sixty-seven were stillborn (3.4 per 1000 births), of which 431 (65%) were preterm. Significant interactions were observed for maternal age, ethnicity, IMD, BMI, parity, smoking, PAPP-A, gestational hypertension, pre-eclampsia and gestational diabetes but not for chronic hypertension and pre-existing diabetes. Stronger associations with term stillbirth were observed in women with obesity compared to BMI 18.5–24.9 kg/m^2 (BMI 30.0–34.9 kg/m^2 term adjusted OR 2.1 [95% CI 1.4–3.0] vs. preterm aOR 1.1 [0.8–1.7]; BMI ≥ 35.0 kg/m^2 term aOR 2.2 [1.4–3.4] vs. preterm aOR 1.5 [1.2–1.8]; p-interaction < 0.01), nulliparity compared to parity 1 (term aOR 1.7 [1.1–2.7] vs. preterm aOR 1.2 [0.9–1.6]; p-interaction < 0.01) and Asian ethnicity compared with White (p-interaction < 0.01).

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A weaker or lack of association with term, compared to preterm, stillbirth was observed for older maternal age, smoking and pre-eclampsia.
Conclusion: Differences in association exist between mothers experiencing preterm and term stillbirth. These differences could contribute to design of timely surveillance and interventions to further mitigate the risk of stillbirth.

1 | Introduction

The World Health Organisation is leading a global drive to reduce perinatal deaths, including stillbirths and neonatal deaths. The Every Newborn Action Plan is an evidence-based initiative to end preventable stillbirths by 2030, with a similar commitment in the 2025 Coverage Targets and Milestones [1, 2].

In the United Kingdom, stillbirth is defined as a baby born with no signs of life after 24 completed weeks of gestation [3, 4] with up to 93% of stillbirths diagnosed before labour [5]. The Office for National Statistics (ONS) in 2021 reported an increase in UK stillbirth rate of 4.1 per 1000 births [6]. Stillbirth significantly affects maternal physical and mental health, impacts the broader family and presents challenges for managing future pregnancies [5, 7, 8].

Whilst factors associated with stillbirth are well described and inform clinical guidance [9–13], they do not distinguish between preterm and term stillbirths. This limits the potential for further targeted clinical intervention and policies to reduce stillbirth rates. Furthermore, there is limited evidence of the impact of clinical guidelines and practices on preterm and term stillbirth rates. This study aimed to identify how maternal and pregnancy characteristics associated with stillbirth differ when stillbirths are stratified by preterm and term gestation.

2 | Methods

2.1 | Study Design and Population

This a secondary cohort analysis of the DESiGN Trial. DESiGN was the first, pragmatic, UK-based, multicentre, cluster-randomised controlled trial in 13 maternity units (clusters) in England. DESiGN compared the growth assessment protocol (GAP) to standard care with a primary outcome of antenatal ultrasound detection of the small-for-gestational-age fetus (SGA) [14–16]. GAP was made available in the United Kingdom by The Perinatal Institute in 2013 [17]. It is a complex intervention aimed at increasing the detection of SGA. It is composed of evidence-based protocols, staff training, customised charts, rolling audits and benchmarking of performance [18]. The trial did not demonstrate a difference in the rate of detection of SGA between GAP and standard care. Findings of the trial have been reported elsewhere [14, 15, 19].

Data from electronic patient records for births between November 2016 and February 2019 were extracted from a baseline trial period (prior to the randomisation), implementation period (when GAP was introduced at intervention clusters following randomisation) and the final comparison period (when outcomes of interest were assessed). The full study protocol and data management processes have also previously been published [14, 16].

This cohort analysis included singleton pregnancies, without major anomalies, born after 24 completed weeks of gestation. We excluded pregnancies without data on birth outcome (livebirth or stillbirth) or gestational age at birth (Figure 1). Data from all 13 clusters were analysed over the full trial period.

2.2 | Exposures and Outcomes of Interest

Maternal and pregnancy characteristics were compared between pregnancies ending in stillbirths and livebirths, with stratification by whether the gestation of birth of a stillborn baby occurred $<37^{+0}$ or $\geq 37^{+0}$ weeks. Preterm birth was defined as a neonate born $>24^{+0}$ and $<37^{+0}$ weeks of gestation. Babies born at term and post-term between 37^{+0} and 42^{+6} weeks' inclusive are classified henceforth as 'term'. Stillbirths were classified 'preterm' or 'term' according to the timing of the birth, as the presumed timing of the intrauterine fetal death or stillbirth diagnosis was not available. Stillbirths were comprised of both antepartum and intrapartum stillbirths, however the routinely collected data did not provide a distinction between these two types.

In determining the risk factors associated with preterm and term stillbirths, we considered the population at risk of these events at the time. In the preterm analysis, preterm stillbirths were compared to a group comprised of preterm livebirths and all babies born $\geq 37^{+0}$ weeks' (whether stillborn or liveborn). Preterm stillbirths were only compared to preterm livebirths when exploring gestational age at birth and birth weight. In the term analysis, term stillbirths were compared to livebirths at term only as the event will necessitate the population at risk to achieve term gestation.

The exposures we explored were selected based on relevant maternal and pregnancy characteristics available from the DESiGN trial. Maternal demographics were self-reported ethnicity (harmonised into the following groups: Asian, Black, Mixed, White and other) and index of multiple deprivation (IMD) quintile (based on postcode of residence). Pregnancy characteristics were maternal age at the end of the first trimester (<20, 20–24, 25–34, 35–39 and ≥40 years), parity (P0, P1, P ≥2), early pregnancy body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9 and ≥35.0 kg/m^2), smoking, pregnancy-associated plasma protein-A (PAPP-A) <0.415 multiples of median (MoM), pre-existing comorbidities (diabetes mellitus, chronic hypertension) and obstetric complications (gestational diabetes [GDM], gestational hypertension and pre-eclampsia).

Characteristics of the babies at birth were reported to describe the characteristics of the population and subgroups. They were

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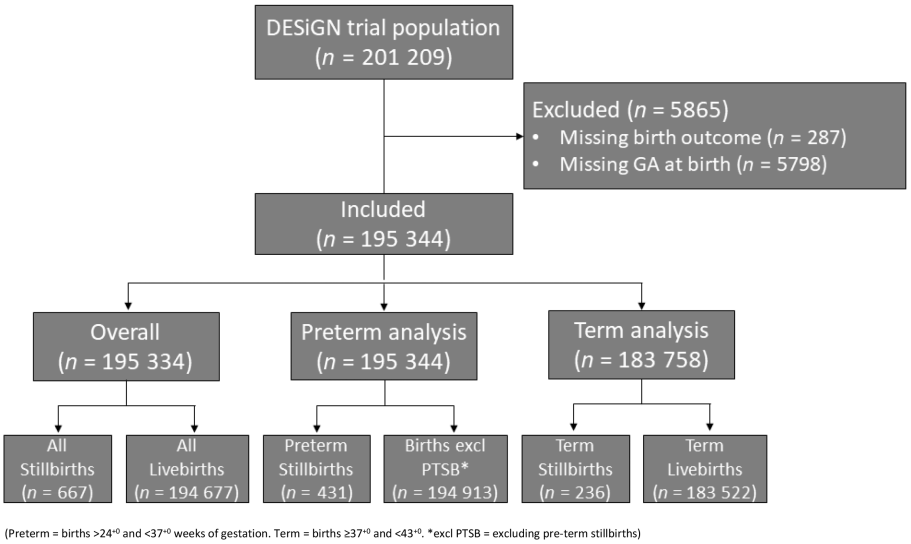

FIGURE 1 | CONSORT flow diagram.

neither included in the multivariable model nor interaction test. These included gestational age at birth and birth weight, including absolute weight and percentile (by British population growth reference [20] or GAP customised [for maternal weight, height, ethnicity and parity] standards [16]).

2.3 | Statistical Analysis

Statistical analyses were performed using Stata MP Version 17 (StataCorp LLC, College Station, TX, USA). All tests were two-sided at a significance level of 0.05.

Distributions of risk factors and other characteristics are described using frequencies, median (interquartile range [IQR]) or mean (standard deviation [SD]) as appropriate, separately by preterm and term and by livebirth and stillbirth.

Multiple imputation of missing exposure data was performed, as previously described [14]. The associations between maternal and pregnancy characteristics and stillbirth were analysed using univariable and multivariable logistic regression models and robust covariance estimates for cluster (by site) correlation, separately for the pre-term and term periods. The rates of stillbirth for each exposure were also reported.

For the multivariable analyses we adjusted for a priori selected confounders relevant to each exposure, that is, plausible causes of the exposure and stillbirth [21], together with the implementation period and arm of the main trial [14, 15] (Table S1). Odds ratios and 95% confidence intervals for the risk of stillbirth for each maternal and pregnancy characteristic were reported. A similar analysis was performed but limited to sites with <50% missing data on PAPP-A, to further explore this variable (a priori selected confounders also in Table S1).

To understand how associations between exposures and stillbirth differed between the preterm and term periods, we fitted a joint model to the combined data to assess for interaction. Women experiencing preterm birth contributed outcome data only for preterm stillbirth, whilst women experiencing a term birth contributed an outcome at both term and preterm. Generalised estimating equations (GEEs) were used to fit logistic regression models for the risk of stillbirth, acknowledging the clustering of outcomes (at term and preterm) for some women. An independence working correlation structure was used to ensure outcomes at term were not implicitly imputed for women with a preterm birth.

3 | Results

The DESiGN trial population included data for 201 209 singleton, nonanomalous births from 13 clusters between November 2016 and February 2019. Records with missing birth outcome (0.1%) or gestational age (2.9%) were excluded (Figure 1). There were 195 344 pregnancies with livebirths and 667 with stillbirths (3.4 per 1000 births) included in the analysis.

The preterm birth rate was 5.9% ($n = 11\,586$): 11 155 livebirths and 431 stillbirths. Preterm stillbirths represented two-thirds (64.6%) of all stillbirths. The rate of preterm stillbirth was 2.2 per 1000 ongoing pregnancies. At term, 238 babies were stillborn (1.3 per 1000 term births) (Figure 1). A breakdown of stillbirths by weeks of gestation is provided in Table S2.

The maternal and pregnancy characteristics of the included pregnancies are summarised in Table 1 by birth outcome and gestational age category at birth. Compared to liveborn babies, stillborn babies were born at a lower median gestational age (29.4 vs. 35.4 weeks' preterm, 39.1 vs. 39.9 weeks' at term). They also had a lower mean birthweight (1307.5 vs. 2316.1 g preterm, 3072.3 vs. 3390.8 g at term) and birthweight percentiles by both population (26.9 vs. 46.9 preterm only, 34.5 vs. 47.2 at term) and customised standards (27.8 vs. 41.3 preterm only, 36.8 vs. 46.7 at term) than liveborn babies.

The interaction tests revealed that for all but two of the potential risk factors considered, there was statistically significant

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TABLE 1 | Maternal and pregnancy characteristics of cohort by birth outcome, stratified by preterm and term births.

	Preterm analysis		Term analysis	
	Preterm stillbirths (*n* = 431)	**Births excluding PTSB (*n* = 194 913)**	**Term stillbirths (*n* = 236)**	**Term livebirths (*n* = 183 522)**
Age at 12 weeks' (years), *n* (%)				
<20	12 (2.8%)	4203 (2.2%)	7 (3.0%)	3903 (2.1%)
20–24	51 (11.8%)	19 313 (9.9%)	20 (8.5%)	18 129 (9.9%)
25–34	211 (49.0%)	106 472 (54.6%)	138 (58.5%)	100 635 (54.8%)
35–39	98 (22.7%)	40 352 (20.7%)	40 (16.9%)	37 869 (20.6%)
≥40	29 (6.7%)	9382 (4.8%)	12 (5.1%)	8606 (4.7%)
Missing	30 (7.0%)	15 191 (7.8%)	19 (8.1%)	14 380 (7.8%)
Ethnicity, *n* (%)				
Asian	91 (21.1%)	36 228 (18.6%)	68 (28.8%)	33 882 (18.5%)
Black	93 (21.6%)	24 167 (12.4%)	46 (19.5%)	22 392 (12.2%)
Mixed	8 (1.9%)	3354 (1.7%)	6 (2.5%)	3148 (1.7%)
White	154 (35.7%)	98 791 (50.7%)	90 (38.1%)	93 721 (51.1%)
Other	39 (9.0%)	16 111 (8.3%)	13 (5.5%)	15 168 (8.3%)
Missing	46 (10.7%)	16 262 (8.3%)	13 (5.5%)	15 211 (8.3%)
IMD quintile, *n* (%)				
1 (least deprived)	30 (7.0%)	24 014 (12.3%)	17 (7.2%)	22 884 (12.5%)
2	38 (8.8%)	24 620 (12.6%)	16 (6.8%)	23 345 (12.7%)
3	72 (16.7%)	41 127 (21.1%)	58 (24.6%)	38 822 (21.2%)
4	178 (41.3%)	62 291 (32.0%)	78 (33.1%)	58 589 (31.9%)
5 (most deprived)	104 (24.1%)	41 044 (21.1%)	63 (26.7%)	38 214 (20.8%)
Missing	9 (2.1%)	1817 (0.9%)	4 (1.7%)	1668 (0.9%)
BMI (kg/m^2), *n* (%)				
<18.5	12 (2.8%)	4311 (2.2%)	1 (0.4%)	4040 (2.2%)
18.5–24.9	117 (27.1%)	78 397 (40.2%)	71 (30.1%)	74 790 (40.8%)
25.0–29.9	90 (20.9%)	44 054 (22.6%)	59 (25.0%)	41 676 (22.7%)
30.0–34.9	45 (10.4%)	18 576 (9.5%)	40 (16.9%)	17 409 (9.5%)
≥35.0	33 (7.7%)	9311 (4.8%)	20 (8.5%)	8620 (4.7%)
Missing	134 (31.1%)	40 264 (20.7%)	45 (19.1%)	36 987 (20.2%)
Parity, *n* (%)				
0	167 (38.7%)	85 069 (43.6%)	114 (48.3%)	80 013 (43.6%)
1	91 (21.1%)	52 605 (27.0%)	42 (17.8%)	49 829 (27.2%)
≥2	119 (27.6%)	33 982 (17.4%)	54 (22.9%)	31 677 (17.3%)
Missing	54 (12.5%)	23 257 (11.9%)	26 (11.0%)	22 003 (12.0%)
PAPP-A < 0.415 MoM, *n* (%)				
Yes (low)	21 (4.9%)	4225 (2.2%)	8 (3.4%)	3772 (2.1%)
No (normal)	111 (25.8%)	70 334 (36.1%)	62 (26.3%)	67 261 (36.7%)
Missing	299 (69.4%)	120 354 (61.7%)	166 (70.3%)	112 489 (61.3%)

(Continues)

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TABLE 1 | (Continued)

	Preterm analysis		Term analysis	
	Preterm stillbirths (*n* = 431)	**Births excluding PTSB (*n* = 194 913)**	**Term stillbirths (*n* = 236)**	**Term livebirths (*n* = 183 522)**
Smoking, *n* (%)	35 (8.1%)	9804 (5.0%)	14 (5.9%)	8903 (4.9%)
Pre-existing co-morbidities, *n* (%)				
Chronic hypertension	9 (2.1%)	2220 (1.1%)	3 (1.3%)	1868 (1.0%)
Pre-existing diabetes	9 (2.1%)	2608 (1.3%)	5 (2.1%)	2239 (1.2%)
Pregnancy complications, *n* (%)				
Gestational hypertension	10 (2.3%)	2264 (1.2%)	2 (0.8%)	2030 (1.1%)
Pre-eclampsia	24 (5.6%)	1934 (1.0%)	6 (2.5%)	1346 (0.7%)
Gestational diabetes	4 (0.9%)	8780 (4.5%)	11 (4.7%)	8135 (4.4%)
Gestational age (weeks), median (IQR)	29.4 (26.0–34.0)	35.4[a] (33.4–36.3)	39.1 (38.1–40.6)	39.9 (39.0–40.7)
Birth weight (g), mean (SD)	1307.5 (761.0)	2316.1 (721.8)[a]	3072.3 (616.0)	3390.8 (462.3)
Missing	7 (1.6%)	156 (1.4%)	0 (0.0%)	253 (0.1%)
Birth weight (pop) percentile, mean (SD)	26.9 (28.3)	46.9 (31.0)[a]	34.5 (30.1)	47.2 (27.0)
Missing	18 (4.2%)	165 (1.5%)	0 (0.0%)	417 (0.2%)
Birth weight (cust) percentile, mean (SD)	27.8 (33.0)	41.3 (33.2)[a]	36.8 (32.8)	46.7 (28.5)
Missing	10 (2.3%)	157 (1.4%)	0 (0.0%)	253 (0.1%)

Abbreviations: cust, customised; IQR, interquartile range; MoMs, multiple of the median; PAPP-A, pregnancy-associated plasma protein-A; pop, population; PTSB, preterm stillbirth; SD, standard deviation.
[a]Preterm analysis restricted to all preterm births only (preterm stillbirths *n* = 431, preterm livebirths *n* = 11 155).

evidence of a different association with risk of stillbirth between the preterm and term periods (Table 2, Figure S1). Chronic hypertension and pre-existing diabetes mellitus were the only associations consistent between gestational periods. For the other associations, the differences were either in the strength of the association, sometimes influenced by a specific exposure category, or in the direction of the association.

For example, compared with a maternal age of 25–34 years, those aged ≥40 years were at significantly increased risk of stillbirth preterm (adjusted odds ratio [aOR] 1.5, 95% CI 1.2–2.0) but not at term (aOR 1.1, 95% CI 0.5–2.4). A significant association of smoking with stillbirth was also observed preterm (aOR 1.6, 95% CI 1.2–2.3) but not at term (aOR 1.3, 95% CI 0.8–2.1). Similarly, pre-eclampsia was significantly associated with stillbirth preterm (aOR 5.3, 95% CI 2.8–10.0) but not at term (aOR 2.8, 95% CI 0.99–8.1).

By contrast, compared with a maternal BMI of 18.5–24.9 kg/m^2, only a BMI of ≥35.0 was significantly associated with increased odds of preterm stillbirth: aOR 1.5 (95% CI 1.2–1.9). Both categories of obesity were significantly, and more strongly, associated with stillbirth at term: BMI 30.0–34.9 aOR 2.1 (95% CI 1.4–3.0) and BMI ≥35.0 aOR 2.2 (95% CI 1.4–3.4).

The differences observed between preterm and term stillbirth for parity appeared to have been driven by differences in opposite directions. Compared with women having 1 previous birth, those with ≥2 previous births had significantly increased odds of stillbirth preterm (aOR 1.5, 95% CI 1.2–1.8) whilst nulliparity only demonstrated a significant association at term (aOR 1.7, 95% CI 1.1–2.7).

A significant interaction was also observed between preterm versus term stillbirth and ethnicity overall, though differences in association are modest for individual ethnicity groups. For example, a somewhat stronger increase in stillbirth risk was seen at term in Asian mothers compared to White (term aOR 2.0 [95% CI 1.4–2.8] vs. preterm aOR 1.6 [95% CI 1.2–2.1]) but the opposite in mothers of Black (preterm aOR 2.5 [95% CI 2.0–3.1] vs. term aOR 2.2 [95% CI 1.7–2.7]) compared to White ethnicity.

Gestational hypertension showed a statistically significant interaction ($p < 0.01$) with potential effects in opposite directions though not statistically significant in either period: preterm stillbirth aOR 1.5 (95% CI 0.8–2.9) and term aOR 0.6 (95% CI 0.2–2.4).

Six clusters had <50% missing values for PAPP-A. Low PAPP-A was found to be significantly associated with preterm stillbirth

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TABLE 2 | Stillbirth rates, univariable and multivariable logistic regression, stratified by preterm and term, with interaction test.

	Preterm stillbirth			Term stillbirth			Interaction test
	SB rate ± 2 SE	OR (95% CI)	aOR (95% CI)	SB rate ± 2 SE	OR (95% CI)	aOR (95% CI)	*p*
Age at 12 weeks' (years)							
<20	2.8 ± 0.2	1.4 (1.2–1.7)	1.5 (0.7–3.2)	1.8 ± 0.1	1.3 (1.0–1.6)	1.2 (0.5–3.2)	
20–24	2.6 ± 0.1	1.3 (1.2–1.5)	1.3 (1.0–1.8)	1.1 ± 0.0	0.8 (0.7–0.9)	0.8 (0.5–1.2)	
25–34	2.0 ± 0.0	Ref	Ref	1.4 ± 0.0	Ref	Ref	<0.01
35–39	2.4 ± 0.0	1.2 (1.1–1.3)	1.3 (1.0–1.6)	1.1 ± 0.0	0.8 (0.7–0.9)	0.8 (0.6–1.1)	
≥40	3.1 ± 0.1	1.6 (1.4–1.8)	1.5 (1.2–2.0)	1.4 ± 0.1	1.0 (0.9–1.2)	1.1 (0.5–2.4)	
Ethnicity							
Asian	2.5 ± 0.0	1.6 (1.5–1.7)	1.6 (1.2–2.1)	2.0 ± 0.0	2.1 (1.9–2.3)	2.0 (1.4–2.8)	
Black	4.0 ± 0.1	2.5 (2.3–2.7)	2.5 (2.0–3.1)	2.0 ± 0.1	2.1 (1.9–2.4)	2.2 (1.7–2.7)	
Mixed	2.4 ± 0.2	1.5 (1.2–1.8)	1.5 (0.6–3.5)	1.8 ± 0.1	1.9 (1.5–2.5)	2.0 (0.8–5.0)	<0.01
White	1.6 ± 0.0	Ref	Ref	0.9 ± 0.0	Ref	Ref	
Other	2.4 ± 0.1	1.5 (1.3–1.7)	1.5 (0.9–2.4)	0.9 ± 0.0	1.0 (0.8–1.2)	0.9 (0.6–1.5)	
IMD quintile							
1 (least deprived)	1.3 ± 0.0	Ref	Ref	0.7 ± 0.0	Ref	Ref	
2	1.6 ± 0.0	1.3 (1.1–1.5)	1.2 (0.6–2.3)	0.7 ± 0.0	0.9 (0.8–1.1)	0.8 (0.4–1.6)	
3	1.8 ± 0.0	1.4 (1.2–1.6)	1.2 (0.7–2.2)	1.5 ± 0.0	2.0 (1.7–2.4)	1.6 (0.8–3.2)	<0.01
4	2.9 ± 0.0	2.3 (2.0–2.6)	1.8 (1.0–3.2)	1.3 ± 0.0	1.8 (1.5–2.1)	1.4 (0.8–2.5)	
5 (most deprived)	2.6 ± 0.0	2.0 (1.8–2.3)	1.4 (0.8–2.6)	1.7 ± 0.0	2.2 (1.9–2.6)	1.7 (0.9–3.0)	
BMI (kg/m^2)							
<18.5	2.4 ± 0.1	1.4 (1.2–1.6)	1.3 (0.8–2.0)	0.5 ± 0.1	0.5 (0.3–0.7)	0.5 (0.2–1.1)	
18.5–24.9	1.8 ± 0.0	Ref	Ref	1.0 ± 0.0	Ref	Ref	
25.0–29.9	2.3 ± 0.0	1.3 (1.2–1.4)	1.2 (1.0–1.4)	1.4 ± 0.0	1.4 (1.3–1.5)	1.4 (1.0–1.9)	<0.01
30.0–34.9	2.6 ± 0.1	1.5 (1.4–1.6)	1.1 (0.8–1.7)	2.2 ± 0.1	2.2 (2.0–2.4)	2.1 (1.4–3.0)	
≥35.0	3.7 ± 0.1	2.1 (1.9–2.3)	1.5 (1.2–1.9)	2.1 ± 0.1	2.2 (1.9–2.5)	2.2 (1.4–3.4)	
Parity							
0	2.0 ± 0.0	1.1 (1.0–1.2)	1.2 (0.9–1.6)	1.4 ± 0.0	1.6 (1.4–1.7)	1.7 (1.1–2.7)	
1	1.8 ± 0.0	Ref	Ref	0.9 ± 0.0	Ref	Ref	<0.01
≥2	3.4 ± 0.1	1.9 (1.8–2.1)	1.5 (1.2–1.8)	1.6 ± 0.0	1.8 (1.6–2.0)	1.6 (0.9–2.7)	
Smoking							
Yes	3.6 ± 0.1	1.7 (1.5–1.9)	1.6 (1.2–2.3)	1.6 ± 0.1	1.2 (1.1–1.5)	1.3 (0.8–2.1)	0.04
No	2.1 ± 0.0	Ref	Ref	1.3 ± 0.0	Ref	Ref	
Pre-existing co-morbidities							
Chronic HTN	4.0 ± 0.2	1.9 (1.5–2.3)	1.5 (0.5–4.2)	1.6 ± 0.2	1.3 (0.9–1.8)	1.0 (0.2–4.3)	0.08
No cHTN	2.2 ± 0.0	Ref	Ref	1.3 ± 0.0	Ref	Ref	

(Continues)

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TABLE 2 | (Continued)

	Preterm stillbirth			Term stillbirth			Interaction test
	SB rate ± 2 SE	OR (95% CI)	aOR (95% CI)	SB rate ± 2 SE	OR (95% CI)	aOR (95% CI)	*p*
Pre-Existing DM	3.4 ± 0.2	1.6 (1.3–1.9)	1.4 (0.5–3.8)	2.2 ± 0.2	1.8 (1.3–2.3)	1.2 (0.1–10.1)	0.53
No DM	2.2 ± 0.0	Ref	Ref	1.3 ± 0.0	Ref	Ref	
Pregnancy complications							
Gestational HTN	4.4 ± 0.3	2.0 (1.7–2.4)	1.5 (0.8–2.9)	1.0 ± 0.1	0.8 (0.5–1.2)	0.6 (0.2–2.4)	<0.01
No gHTN	2.2 ± 0.0	Ref	Ref	1.3 ± 0.0	Ref	Ref	
Pre-eclampsia	12.3 ± 0.4	5.9 (5.2–6.7)	5.3 (2.8–10.0)	4.4 ± 0.3	3.5 (2.8–4.5)	2.8 (1.0–8.1)	<0.01
No PE	2.1 ± 0.0	Ref	Ref	1.3 ± 0.0	Ref	Ref	
Gestational DM	0.5 ± 0.0	0.2 (0.1–0.3)	0.2 (0.1–0.3)	1.4 ± 0.1	1.1 (0.9–1.3)	0.9 (0.5–1.5)	<0.01
No GDM	2.3 ± 0.0	Ref	Ref	1.3 ± 0.0	Ref	Ref	

Note: SB rate = number of stillbirths per 1000 births, restricted to term births only at term; aOR = adjusted odds ratio (exposures adjusted for a priori selected confounders [age: ethnicity, IMD, parity; ethnicity: n/a, IMD: age, ethnicity, parity, pre-existing co-morbidities; BMI: age, ethnicity, IMD, parity, smoking, pre-existing co-morbidities; parity: age, ethnicity, IMD, BMI, pre-existing co-morbidities; smoking: age, ethnicity, IMD, parity, pre-existing co-morbidities; cHTN/pre-existing DM: all variables except cHTN/pre-existing DM, respectively, and pregnancy complications; gHTN/PE/GDM: all variables except gHTN/PE/GDM respectively]; also described in Table S1), as well as the implementation period and arm of main trial.
Abbreviations: BMI, body mass index; cHTN, chronic hypertension; DM, diabetes mellitus; GDM, gestational diabetes mellitus; gHTN, gestational hypertension; HTN, hypertension; IMD, index of multiple deprivation.

(aOR 2.8, 95% CI 2.0–3.9), in a multivariable model restricted to the six clusters. A weaker positive association, not statistically significant, was observed at term (aOR 2.2, 95% CI 0.6–7.5). The interaction test showed a significant difference between the relationship of PAPP-A to preterm and term stillbirth ($p < 0.01$).

4 | Discussion

4.1 | Main Findings

We demonstrated significantly different associations with stillbirth risk between preterm and term periods for 10 of 12 exposures explored. Differences driven by weaker associations with stillbirth at term may reflect national guidance advocating earlier term birth (e.g., older maternal age, pre-eclampsia) [9, 10, 12]. Differences driven by stronger associations at term (e.g., obesity, nulliparity and ethnicity) lacked clear guidance on timing of birth.

4.2 | Strengths and Limitations

To our knowledge, this is the first large cohort analysis in a high-income setting to directly compare associations of multiple maternal and pregnancy risk factors with stillbirth at term compared to preterm. Previous large-scale studies and reports have not distinguished between independent risk factors for preterm and term stillbirth [5, 22]. This limited our understanding of the drivers of these events and the influences of clinical practice and policy. Notably, preterm birth rates, stillbirth rates and preterm stillbirth proportions were similar to national data, supporting the generalisability of our results to the UK population [5, 6, 22].

Limitations include heterogeneously recorded electronic data, potentially resulting in misclassification [17]. Missing PAPP-A data prevented exploration of its associations with preterm and term stillbirth in the primary models. Most stillbirths (65%) occurred preterm, consistent with MBRRACE [5], limiting the power to detect associations at term. Our term stillbirth findings should therefore be treated with caution and replication of our results in a larger sample would be valuable. We limited factors explored to those available in DESiGN, focusing on established correlates and risk factors for stillbirth. We could not assess unmeasured risk factors, such as passive smoking or intrahepatic cholestasis of pregnancy, nor explore novel emerging potential risk factors, such as electronic cigarettes, or molecular mechanisms [23–27]. Gestational age of intrauterine demise was not routinely recorded, therefore some term stillbirths may have died late preterm. With respect to gestational age at birth amongst live and stillbirths, we highlight that this provides a descriptive overview rather than inferring association or causality. Whilst it has previously been suggested that birth usually occurs within 2 days of demise [28], there is a need for cautious interpretation of our findings. Without a known interval between demise and birth, we may overestimate the prevalence of SGA in stillbirths. Although we lacked data on stillbirth aetiology, the data provided a unique opportunity to analyse multiple maternal and pregnancy factors.

4.3 | Interpretation

Some known risk factors differed in their associations between preterm and term stillbirth through an increased risk with preterm stillbirth and a weaker, or lack of, association with term stillbirth. These included older maternal age, smoking and

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pre-eclampsia. The weaker association at term should not be interpreted as a direct biological effect that is limited to preterm birth. Clinical guidelines advise increased surveillance, smoking cessation support and planned timely birth, such as with older maternal age, smoking and hypertensive disorders [10–12, 29]. If these findings relate to mitigation through enhanced intervention, this is reassuring as national guidelines are achieving their goal at term.

We observed a low incidence of GDM in the preterm population, a condition selectively screened for up to 28 weeks' in the United Kingdom. Many GDM cases are diagnosed later in pregnancy through screening or when fetal macrosomia or polyhydramnios are suspected, or postnatally during stillbirth investigation. Thus, many preterm stillbirths occur before GDM diagnosis or development, explaining the low incidence of GDM in the preterm group. The lack of association between GDM and term stillbirth in our cohort is similarly likely to reflect robust national guidance on earlier term birth in these women [9].

Our findings highlight the need to review existing evidence and guidance on birth timing to mitigate term stillbirth. Women with risk factors lacking guidelines for earlier birth, such as obesity, remain at higher risk of term stillbirth [30]. Earlier term births (from 37 to 39 weeks') in pregnant individuals with obesity have been proposed to reduce perinatal morbidity without increasing caesarean rates or adverse outcomes [31–33]. A retrospective cohort study of 2862 stillbirths demonstrated increased perinatal mortality after 38 weeks' at BMI ≥40 kg/m^2, recommending birth at this gestation [32]. Gestational cutoffs were less clear for BMI <40 kg/m^2 and the authors did not adjust for confounding factors such as maternal age, ethnicity and parity. A systematic review and meta-analysis of 16 274 stillbirths found modest maternal BMI increases also raised stillbirth risk [34]. Further guidance on fetal growth surveillance and birth timing in women with obesity is needed, as well understanding stillbirth mechanisms in this group. Differences for parity showed nulliparous women at weaker preterm stillbirth risk, whilst multiparous women had increased adjusted odds of stillbirth both preterm and at term, compared to mothers with one previous birth. Existing guidelines only recognise nulliparity as a stillbirth risk factor [11, 12, 35, 36]. Further studies are needed to better understand the increased risk in multiparous women. Stillbirth risk differences were not consistent across ethnicities nor deprivation indices. A national cohort study of over 1.2 million women in England linked socioeconomic and ethnic inequalities to a substantial proportion of stillbirths, stressing the need for targeted prevention efforts, again highlighted in the Saving Babies Lives Care Bundle [13, 22]. Our study supports targeted surveillance and an improved understanding of factors influencing antenatal choices for safer pregnancies.

Preterm stillbirth risk mitigation requires a different approach, as the risks of elective preterm birth rarely outweigh the benefits. Preterm stillbirth, compared to term, is predominantly caused by placentally mediated pathology and can potentially be predicted by mid-trimester evaluation of maternal risk factors, estimated fetal weight (EFW) and uterine artery pulsatility index [8]. Aspirin, due to its role in reducing other placentally mediated diseases, could reduce perinatal mortality in high-risk women [37, 38]. However, in progressive conditions, such as pre-eclampsia, late preterm birth may be justified to reduce maternal morbidity and prevent stillbirths [39, 40]. The longer-term consequences of prematurity must also be considered.

5 | Conclusion

We identified differences in several maternal and pregnancy factors associated with preterm and term stillbirths, with 'term' defined as those occurring at or after 37 weeks of gestation. Clear national guidance on birth timing for at-risk mothers, especially those with obesity, may reduce stillbirth rates. Consideration of differences existing between preterm and term stillbirth can drive our understanding of mechanisms leading to stillbirth, enabling the development of screening, prevention strategies and tailored interventions to mitigate stillbirth risk.

Author Contributions

D.P. is the Chief Investigator of the DESiGN trial. C.W., J.E., M.C.V., S.R., A.C. and D.P. designed this study. C.W. and J.E. conducted the analysis. C.W., J.E., M.C.V., S.R., D.A.L., A.C. and D.P. reviewed and interpreted the results. C.W. and J.E. drafted the manuscript. All authors have reviewed the draft manuscript, provided feedback, read and approved the final version of the manuscript.

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Ethics Statement

Ethical approval for the DESiGN trial was obtained through the Health Research Authority (HRA) Integrated Research Applications System (IRAS) from the London Bloomsbury Research Ethics Committee (Ref. 15/LO/1632) and the Confidentiality Advisory Group (Ref. 15/CAG/0195). King's College London is the sponsor for this trial. Individual informed consent was not obtained however women could opt out from sharing their data.

Conflicts of Interest

M.C.V. was supported by CAPES (BEX 9571/13-2). S.R., K.C., A.H. and J.S. were supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust. D.A.L.'s contributions were supported by the Bristol NIHR Biomedical Research Centre and her NIHR Senior Investigator Award (NF-0616-10102). D.A.L. has received support from Medtronic Ltd. and Roche Diagnostics for research unrelated to that presented here and that ended 5 years or more ago. D.A.L.'s contribution is supported by the UK Medical Research Council (MC_UU_00032/05) and the British Heart Foundation (CH/F/20/90003). J.S. is supported by an NIHR Senior Investigator Award. N.M. reports personal fees from

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Takeda, personal fees from RSM Consulting, personal fees from Novartis, outside the submitted work. N.M. receives a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme at UCLH/UCL. B.T. is the Clinical Director and J.S. is a programme lead of the Tommy's National Centre for Maternity Improvement based at the Royal College of Obstetrics and Gynaecology; the Centre's objective is to translate the latest evidence into clinical practice in the United Kingdom. J.S. is Head of Maternity and Midwifery Research at NHS England. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. World Health Organisation, "Every Newborn: An Action Plan to End Preventable Deaths" [Internet], 2014, https://www.who.int/docs/default-source/mca-documents/advisory-groups/quality-of-care/every-newborn-action-plan-(enap).pdf?sfvrsn=4d7b389_2.

2. "Launch of the Every Newborn Action Plan: 2025 Coverage Targets and Milestones" [Internet], accessed February 27, 2023, https://www.who.int/news/item/28-08-2020-launch-of-the-every-newborn-action-plan-2025-coverage-targets-and-milestones.

3. United Kingdom, "Still-Birth Definition Act 1992 [16 March 1992]," Curr Law Statut Annot GB 2(1992):29-1–29-3.

4. Office for National Statistics, "Birth Characteristics in England and Wales: 2020 Edition of This Dataset" [Internet], 2022, https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/datasets/birthcharacteristicsinenglandandwales.

5. NPEU, "MBRRACE-UK Perinatal Mortality Surveillance Report for Births in 2020" [Internet], 2021, https://www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/perinatal-surveillance-report-2020/MBRRACE-UK_Perinatal_Surveillance_Report_2020.pdf.

6. "Child Mortality (Death Cohort) Tables in England and Wales—Office for National Statistics" [Internet], accessed April 21, 2023, https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/childmortalitystatisticschildhoodinfantandperinatalchildhoodinfantandperinatalmortalityinenglandandwales.

7. A. E. P. Heazell, D. Siassakos, H. Blencowe, et al., "Stillbirths: Economic and Psychosocial Consequences," *Lancet* 387, no. 10018 (2016): 604–616.

8. G. Ashoor, A. Syngelaki, I. Papastefanou, K. H. Nicolaides, and R. Akolekar, "Development and Validation of Model for Prediction of Placental Dysfunction-Related Stillbirth From Maternal Factors, Fetal Weight and Uterine Artery Doppler at Mid-Gestation," *Ultrasound in Obstetrics and Gynecology* 59, no. 1 (2022): 61–68.

9. NICE, *Diabetes in Pregnancy: Management From Preconception to the Postnatal Period* (Ra'anana, Israel: NICE, 2020).

10. "Induction of Labour at Term in Older Mothers" (Scientific Impact Paper No. 34) | RCOG [Internet], 2013, https://rcog.org.uk/guidance/browse-all-guidance/scientific-impact-papers/induction-of-labour-at-term-in-older-mothers-scientific-impact-paper-no-34/.

11. "Small-for-Gestational-Age Fetus, Investigation and Management" (Green-Top Guideline No. 31) [Internet] (London, UK: Royal College of Obstetrics and Gynaecology, 2013), https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_31.pdf.

12. Nice, "Hypertension in Pregnancy: Diagnosis and Management" (NICE Guideline NG133) [Internet], 2019, https://www.nice.org.uk/guidance/NG133.

13. NHS England, "Saving Babies' Lives Version Three: A Care Bundle for Reducing Perinatal Mortality" [Internet], accessed July 5, 2023, https://www.england.nhs.uk/publication/saving-babies-lives-version-three/.

14. S. Relph, M. Elstad, B. Coker, et al., "Using Electronic Patient Records to Assess the Effect of a Complex Antenatal Intervention in a Cluster Randomised Controlled Trial—Data Management Experience From the DESiGN Trial Team," *Trials* 22, no. 1 (2021): 195.

15. M. C. Vieira, S. Relph, W. Muruet-Gutierrez, et al., "Evaluation of the Growth Assessment Protocol (GAP) for Antenatal Detection of Small for Gestational Age: The DESiGN Cluster Randomised Trial," *PLoS Medicine* 19, no. 6 (2022): e1004004, https://doi.org/10.1371/journal.pmed.1004004.

16. M. C. Vieira, S. Relph, A. Copas, et al., "The DESiGN Trial (DEtection of Small for Gestational Age Neonate), Evaluating the Effect of the Growth Assessment Protocol (GAP): Study Protocol for a Randomised Controlled Trial," *Trials* 20, no. 1 (2019): 1–14.

17. S. Clifford, S. Giddings, M. Southam, M. Williams, and J. Gardosi, "The Growth Assessment Protocol: A National Programme to Improve Patient Safety in Maternity Care," *MIDIRS Midwifery Digest* 23, no. 4 (2013): 516–523.

18. "Perinatal Institute: Programme" [Internet], accessed February 27, 2023, https://perinatal.org.uk/GAP/Programme.

19. S. Relph, M. C. Vieira, A. Copas, et al., "Improving Antenatal Detection of Small-for-Gestational-Age Fetus: Economic Evaluation of Growth Assessment Protocol," *Ultrasound in Obstetrics and Gynecology* 60, no. 5 (2022): 620–631.

20. T. J. Cole, J. V. Freeman, and M. A. Preece, "British 1990 Growth Reference Centiles for Weight, Height, Body Mass Index and Head Circumference Fitted by Maximum Penalized Likelihood," *Statistics in Medicine* 17 (1998): 407–429.

21. G. Bandoli, K. Palmsten, C. D. Chambers, L. L. Jelliffe-Pawlowski, R. J. Baer, and C. A. Thompson, "Revisiting the Table 2 Fallacy: A Motivating Example Examining Preeclampsia and Preterm Birth," *Paediatric and Perinatal Epidemiology* 32, no. 4 (2018): 390–397.

22. J. Jardine, K. Walker, I. Gurol-Urganci, et al., "Adverse Pregnancy Outcomes Attributable to Socioeconomic and Ethnic Inequalities in England: A National Cohort Study," *Lancet* 398, no. 10314 (2021): 1905–1912.

23. J. Girling, C. L. Knight, and L. Chappell, "Intrahepatic Cholestasis of Pregnancy: Green-Top Guideline No. 43 June 2022," *BJOG: An International Journal of Obstetrics and Gynaecology* 129, no. 13 (2022): e95–e114.

24. P. K. Xaverius, Z. O'reilly, A. Li, L. H. Flick, and L. D. Arnold, "Smoking Cessation and Pregnancy: Timing of Cessation Reduces or Eliminates the Effect on Low Birth Weight," *Maternal and Child Health Journal* 23 (2019): 1434–1441, https://doi.org/10.1007/s10995-019-02751-2.

25. R. O. Bahado-Singh, A. Syngelaki, R. Mandal, et al., "First-Trimester Metabolomic Prediction of Stillbirth," *Journal of Maternal-Fetal & Neonatal Medicine* 32, no. 20 (2019): 3435–3441.

26. A. K. Regan, J. M. Bombard, M. M. O'Hegarty, R. A. Smith, and V. T. Tong, "Adverse Birth Outcomes Associated With Prepregnancy and Prenatal Electronic Cigarette Use," *Obstetrics and Gynecology* 138, no. 1 (2021): 85–94.

27. D. M. Gallo, W. Fitzgerald, R. Romero, et al., "Proteomic Profile of Extracellular Vesicles in Maternal Plasma of Women With Fetal Death," *Journal of Maternal-Fetal & Neonatal Medicine* 36, no. 1 (2023): 2177529.

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28. J. Gardosi, T. Mul, M. Mongelli, and D. Fagan, "Analysis of Birthweight and Gestational Age in Anteparturn Stillbirths," *BJOG: An International Journal of Obstetrics and Gynaecology* 105, no. 5 (1998): 524–530.

29. NICE, *Diabetes in Pregnancy: Management From Preconception to the Postnatal Period (NICE Guideline NG3)* (Ra'anana, Israel: NICE, 2020).

30. F. C. Denison, N. R. Aedla, O. Keag, et al., "Care of Women With Obesity in Pregnancy: Green-Top Guideline No. 72," *BJOG: An International Journal of Obstetrics and Gynaecology* 126, no. 3 (2018): e62–e106.

31. V. R. Lee, B. G. Darney, J. M. Snowden, et al., "Term Elective Induction of Labour and Perinatal Outcomes in Obese Women: Retrospective Cohort Study," *BJOG: An International Journal of Obstetrics and Gynaecology* 123, no. 2 (2016): 271–278.

32. R. Yao, B. L. Schuh, and A. B. Caughey, "The Risk of Perinatal Mortality With Each Week of Expectant Management in Obese Pregnancies," *Journal of Maternal-Fetal & Neonatal Medicine* 32, no. 3 (2019): 434–441, https://doi.org/10.1080/14767058.2017.1381903.

33. L. Gill and M. Holbert, "Computational Model for Timing of Delivery in An Obese Population," *Journal of Maternal-Fetal & Neonatal Medicine* 31, no. 4 (2018): 469–473, https://doi.org/10.1080/14767058.2017.1288207.

34. D. Aune, O. D. Saugstad, T. Henriksen, and S. Tonstad, "Maternal Body Mass Index and the Risk of Fetal Death, Stillbirth, and Infant Death: A Systematic Review and Meta-Analysis," *JAMA: The Journal of the American Medical Association* 311, no. 15 (2014): 1536–1546.

35. G. Gardener, M. Weller, E. Wallace, et al., "Position Statement: Detection and Management of Fetal Growth Restriction in Singleton Pregnancies [Internet]," *Perinatal Society of Australia and New Zealand/Stillbirth Centre of Research Excellence* (2018), https://ranzcog.edu.au/wp-content/uploads/2022/05/Detection-and-Management-of-Women-With-Fetal-Growth-Restriction-in-Singleton-Pregnancies.pdf.

36. "Antepartum Haemorrhage" (Green-top Guideline No. 63) | RCOG [Internet], 2011, https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/antepartum-haemorrhage-green-top-guideline-no-63/.

37. D. L. Rolnik, D. Wright, L. C. Poon, et al., "Aspirin Versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia," *New England Journal of Medicine* 377, no. 7 (2017): 613–622.

38. M. K. Hoffman, S. S. Goudar, B. S. Kodkany, et al., "Low-Dose Aspirin for the Prevention of Preterm Delivery in Nulliparous Women With a Singleton Pregnancy: A Randomised Multi-Country Placebo Controlled Trial," *Lancet* 395, no. 10220 (2020): 285.

39. L. C. Chappell, P. Brocklehurst, M. E. Green, et al., "Planned Early Delivery or Expectant Management for Late Preterm Pre-Eclampsia (PHOENIX): A Randomised Controlled Trial," *Lancet* 394, no. 10204 (2019): 1181–1190.

40. A. Beardmore-Gray, N. Vousden, P. T. Seed, et al., "Planned Delivery or Expectant Management for Late Preterm Pre-Eclampsia in Low-Income and Middle-Income Countries (CRADLE-4): A Multicentre, Open-Label, Randomised Controlled Trial," *Lancet* 402 (2023): 386–396, https://doi.org/10.1016/S0140-6736.

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